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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,970	09/26/2001	Horst Lindholfer	080575-00000	1046

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EXAMINER

HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/787,970

Applicant(s)

LINDHOLFER ET AL.

Examiner

Larry R. Helms

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 July 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-36 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>9/26/01 10/4/01</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Upon further review the species requirement is vacated.
2. Claims 1-36 are under examination.

Specification

3. The disclosure is objected to because of the following informalities:

Page 11, line 30 recites "Claim 1" and this reference to the claims in the specification need to be removed.

Appropriate correction is required.

Claim Objections

4. Claims 26 (and 27 which depends from 26) are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 26 depends on claim 25 wherein both claims recite an interval of 1-6 hours.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-36 are indefinite for reciting "tumor cell" in claim 1 (b) because it is not clear if the antigen is on the autologous or allogenic tumor or some other tumor.

b. Claim 3 and those dependent from claim 3 are indefinite for reciting "interval" and depending on claim 1 because there is no antecedent basis for the term. There is no interval recited in claim 1.

c. Claim 17 and those depending on claim 17 are indefinite for reciting "inducible" and "uninduced state (normal state)" because it is not clear what the terms and phrases mean. Is the "inducible" state the tumor state or cells that are tumorigenic or has the tumor cells been modified? In addition what is a "normal state", a non tumor state?

d. Claims 17 and those dependent on claim 17 are indefinite for reciting "inducible" because it is unclear what an inducible antigen is. Is expressing an antigen via a vector added to the tumor cells an inducible antigen? It is unclear what the antigen is or what induces it.

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Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berd (US Patent 6,458,369, with priority to 5/98) and further in view of Lindhofer et al [a] (Blood 88:4651-4658, 1996, IDS 9/26/01) and Lindhofer et al [b] (US Patent 6,551,592,

filed 9/97) and Multihoff et al (Int. J. Cancer 61:272-279, 1995) and Jedlitschky et al (US Patent 6,235,785, 2/97).

The claims are summarized as a method of inducing immunity against a tumor by administering 2-4 hours apart 1) autologous or alogenic tumor cells treated by radiation at about 50-200 Gy or mitomycin C to prevent their survival after refusion and 2) a bispecific antibody of claimed isotypes that bind to T cell, bind to tumor antigen CD3 or HSP72 or 90, and bind via their Fc portion, wherein the antibodies are administered at about 5-500 micrograms, and the tumor cells are at 10^8 cells.

Berd teach methods of treating tumors by addition of modified autologous tumor cells treated with radiation to prevent their survival after injection and the method can be used in conjunction with antibody therapy consecutively (see entire document, and column 9, 10, 12). Berd does not teach additional treatment with a bispecific antibody or treatment of the tumor cells with mitomycin C. These deficiencies are made up for in the teachings of Lindhofer [a], Lindhofer [b], Multhoff et al, and Jedlitschky et al.

Lindhofer [a] teach treatment of tumors with a bispecific antibody that binds CD3 on T cells and a tumor antigen.

Lindhofer [b] teach bi and trispecific antibodies with the claimed isotype and binding properties of CD3, CD2, CD28, CD4, CD8, CD6, CD5, and inducing cytokines for inducing anti-tumor immunity (see entire document).

Multhoff et al teach HSP72 and 90 are expressed in tumors and not on normal cells.

Jedlitschky et al teach mitomycin C was known as a chemotherapeutic agent to treat tumors (see column 7).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have added autologous treated tumor cells and bispecific antibodies to T cells and a tumor antigen or a HSP protein at different times of from 2-4 hours for inducing an immune response in view of the references.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have added autologous treated tumor cells and bispecific antibodies to T cells and a tumor antigen or a HSP protein at different times of from 2-4 hours for inducing an immune response in view of the references because Berd teach adding tumor cells treated with radiation and administered to a cancer patient to elicit T cells and eliciting an immune response and the method can be used consecutively with antibody therapy. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have added autologous treated tumor cells and bispecific antibodies to T cells and a tumor antigen or a HSP protein at different times of from 2-4 hours for inducing an immune response in view of the references because Lindhofer [a] teach addition of bispecific antibodies to treat cancer wherein the antibody binds to a T cell. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have added autologous treated tumor cells and bispecific antibodies to T cells and a tumor antigen or a HSP protein at different times of from 2-4 hours for inducing an immune response in view of the references because Lindhofer [b] teach bi and

trispecific antibodies to induce immunity and these antibodies have the characteristics claimed and can redirect T cells to tumor cells expressing the tumor antigen and it would have been obvious to use either a tumor antigen or a HSP protein because Multhoff et al teach that heat-shock proteins are on tumor cells similar to tumor antigens and in fact these can be used to elicit an anti-tumor immune response (see page 278). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have added autologous treated tumor cells and bispecific antibodies to T cells and a tumor antigen or a HSP protein at different times of from 2-4 hours for inducing an immune response in view of the references because as taught by Jedlitschky et al mitomycin C was known as a chemotherapeutic agent and it would have been obvious to use it to treat the cancer cells and to prevent the survival upon re-administration just as Berd did with radiation. Thus, it would have been obvious to add treated tumor cells prior to administration of a bispecific antibody with the characteristics claimed because the tumor cells increase the T cells and the bispecific antibodies bind the T cell and the tumor cells to initiate an immune response against the tumor.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

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unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-36 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of copending Application No. 10/378218. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims in the instant application are directed to specific bispecific antibodies and treated tumor cells administered from 2-4 hours for inducing an immune response and the claims would anticipate the claims in the 10/378218 application directed to use of a compositions having a bispecific antibody for destruction of tumor cells and addition of inactivated tumor cells administered after the antibodies.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-36 directed to an invention not patentably distinct from claims 1-24 of commonly assigned 10/378218. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP

§ 2302). Commonly assigned 10/378218, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Conclusion

11. No claim is allowed.


12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Siew, can be reached at (571) 272-0787.

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13. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 703-872-9306.

Larry R. Helms

571-272-0832



LARRY R. HELMS, PH.D
PRIMARY EXAMINER